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Stem Cell Exhaustion and Reduced Tissue Repair in Ageing, Cancer, and Degenerative Diseases

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***Abstract*—Stem cell exhaustion - the loss of functional stem cell numbers and their regenerative capacity - is a central trademark for cellular ageing and a key contributor to impaired and affected tissue repairs in many degenerative diseases and cancer. This paper will discuss the cellular and molecular understanding of the mechanisms that drive stem dysfunction (DNA damage, condensation of telomeres) and examine how exhaustion contributes to degenerative diseases such as Alzheimer's.**

I. INTRODUCTION

Ageing is an inevitable biological process affecting all living organisms. As we grow older, our cells gradually lose their ability to function, divide, and repair themselves. This decline occurs gradually over time, eventually leading to tissue and organ weakening. On a molecular level, it results in less resilient tissues and a greater risk of diseases such as cancer, heart disease, and other neurological disorders like Alzheimer's.

Every tissue in our body comprises many specialised cells that perform specific tasks—such as muscle cells that contract or nerve cells that transmit signals. However, these cells cannot divide indefinitely. To maintain tissue health, the body relies on stem cells, which are unique cells capable of self-renewal and differentiation—meaning they can replicate themselves and generate new specialised cells. Stem cells are essential for tissue repair, regeneration, and maintenance throughout life.

Over time, however, stem cells themselves also begin to age. They accumulate DNA damage due to shortening of telomeres and experience stress from their environment, gradually losing their ability to divide and respond to signals that normally activate them. This process, known as stem cell exhaustion, is one of the main reasons why older tissues do not heal as well as they used to. Stem cell exhaustion is now recognised as one of the key hallmarks of ageing, along with other processes like DNA damage, telomere shortening and mitochondrial dysfunction.

These age-related cellular changes are deeply connected to the development of diseases. In degenerative diseases like Alzheimer's or Parkinson's, the gradual failure of neural stem cells leads to reduced replacement of lost neurons and impaired repair of brain tissue. As a result, memory and other cognitive functions begin to decline. Similarly, in the muscles and bones, ageing stem cells contribute to sarcopenia (loss of muscle mass) and osteoporosis (weakening of bones).

The same mechanisms that cause stem cells to lose their function over time also slowly contribute to cancer. In some cases, when cells experience DNA damage and lose control over their growth signals, they can start to divide uncontrollably, forming tumours. Most of such cells die, but a few cells retain such properties that they can escape growth limits and continuously divide, cells that regenerate tumours. Such cells are marked as cancer stem cells. This shows how cellular ageing can weaken both healthy tissue and increase the risk of cancer.

Having established the importance of stem cells in the role of tissue regeneration, this section examines how ageing alters stem cell function and why it is detrimental to the human animal. The following review explores the biological basis of stem cell exhaustion, its underlying mechanisms, and its implications for diseases associated with ageing.

Introduction to Stem Cells

Stem cells are responsible for sustaining tissue homeostasis throughout life through their capacity for self-renewal and differentiation. As Sharpless and DePinho(2007) note, "we age, in part, because our self-renewing stem cells grow old as a result of heritable intrinsic events, such as DNA(Deoxyribonucleic Acid) damage, as well as extrinsic forces, such as changes in their supporting niches"(1)

Stem cells maintain the continuous renewal of tissue such as skin, intestinal lining, etc. In the case of any

damage occurring or any injury, the stem cells divide and replace the damaged and/or dead cells, ensuring proper tissue function. Without efficient stem cell activity, our body's natural healing process slows, and tissues lose structural and functional integrity. Stem cells preserve tissue integrity through two main functions: normal renewal and regeneration after injury. Under steady conditions, stem cells divide slowly to replace worn-out or dead cells, sustaining tissue homeostasis. When damage occurs, they are activated to proliferate and differentiate rapidly to restore lost or injured cells. Therefore, stem cells are essential not only for normal tissue maintenance but also for regeneration following damage, making their decline with age a central feature of ageing and disease.

There are three categories of stem cells: Mesenchymal Stem Cells (MSCs), Neural Stem Cells (NSCs), and Hematopoietic Stem Cells (HSCs). The property of re-establishing hematopoiesis with persistent maintenance of homeostasis through a balance of cell self-renewal and differentiation defines HSCs.(2)

It is typified by the potential of regenerating the stem cell pool based on self-renewal, simultaneously generating differentiated cell lineages of various types. (3)

MSCs have demonstrated promise in several areas, such as tissue regeneration, immunological modulation, anti-inflammatory qualities, and wound healing. (4)

These cells, when transplanted, can modulate both the host immune response to injury as well as direct neural stem cells and progenitors to differentiate along lineages that support rather than inhibit regeneration. (5)

NSCs represent an important source of stem cells from the brain that can differentiate into neurons, oligodendrocytes or astrocytes, and they are responsible for neurogenesis in the human adult brain. (6)

II. MECHANISM OF STEM CELL EXHAUSTION

With advancing age, stem cells progressively lose their regenerative potential due to intrinsic and extrinsic factors. They lose the ability to sustain tissue homeostasis and regeneration. Although some stem cells are relatively shielded from some cellular ageing mechanisms compared to their differentiated progeny, they remain vulnerable to both intrinsic and extrinsic stressors. Recent research has delineated several key mechanisms contributing to stem cell exhaustion:

1. Genomic Instability and DNA Damage
   Accumulation of DNA damage is a primary intrinsic factor leading to stem cell exhaustion. Telomere attrition mutations in DNA repair pathways compromise the genomic integrity of stem cells, limiting their proliferative capacity and increasing susceptibility. As noted by Thomas A.Rando(2025), “Aged stem cells exhibit increased DNA damage, impaired DNA repair mechanisms, and diminished capacity for self-renewal”. (7)
2. Epigenetic Alterations
   Epigenetic changes, like alterations in DNA methylation patterns and histone modifications, disturb gene expression regulation in aged stem cells. These changes can cause abnormal differentiation and the loss of stem identity. Epigenetic by-products of stem cells contribute to ageing by disrupting gene expression programs important for self-renewal and differentiation. (8)
3. Mitochondrial Dysfunction
   Mitochondrial dysfunction results in increased production of reactive oxygen species (ROS), leading to oxidative stress and cellular damage. This stress accelerates ageing processes in stem cells. According to a paper written by Shuaifei Ji, “Mitochondrial dysfunction and ROS accumulation are central to the ageing of stem cells, impairing their regenerative capacity” (9)
4. Altered Niche and Microenvironment
   The stem cell niche comprises various cell types and extracellular matrices; it plays an important role in maintaining stem cell function. Age-associated changes in the stem cell niche, such as increased inflammation and altered cell signalling, contribute to stem cell exhaustion. (10)
5. Accumulation of Senescent Cells

The accumulation of senescent cells (ageing cells that have permanently stopped dividing but do not die) within tissues secretes pro-inflammatory substances that disrupt tissue homeostasis and impair cellular function. These senescent cells create a hostile environment that accelerates ageing by damaging healthy cells and is a significant hallmark in age-related diseases such as osteoarthritis and Alzheimer's. (11)

III. SYSTEMIC DISEASES AS A CONSEQUENCE OF STEM CELL EXHAUSTION

Stem cell exhaustion represents one of the most prevalent mechanisms linking ageing to multiple genetic diseases. In skeletal muscle, for instance, stem cell decline is directly correlated with a loss of strength and decreased muscle tissue repairability. A 2025 review in Stem Cell Research and Therapy reports that satellite cells exhibit disrupted activation and differentiation in aged muscle due to senescence and immune infiltration. (12) A recent Stanford study, supporting this finding, found that restoring youthful prostaglandin E2 signalling, combined with exercise, reestablished epigenetic balance and improved muscle regeneration in old mice. (13) Neural stem cells show a comparable pattern. A UCLA group demonstrated that ageing neural progenitors in the subventricular zone lose proliferative capacity through epigenetic silencing of growth-associated genes rather than lineage switching. (14)

Likewise, a review of hippocampal neurogenesis emphasised that oxidative stress and inflammatory signalling within the ageing niche drastically reduce neuronal output. (15) Joint degeneration follows the same logic: osteoarthritic cartilage shows reduced mesenchymal stromal-cell function, though in vitro experiments reveal that microRNA-122-5p carried by MSC-derived vesicles can rejuvenate chondrocyte autophagy and repair capacity. (16) These tissue-specific failures illustrate a broader biological pattern–stem cell exhaustion as a systemic driver to disease. When regenerative pools across multiple organs begin to falter simultaneously, the body loses its capacity to repair, adapt and maintain homeostasis. As López-Otín et al. describe, "the exhaustion of stem cells compromises tissue homeostasis and regeneration, leading to functional decline" (17). This is most evident in our blood and immune systems. Also, there is an age-related gradual functional decline of hematopoietic stem cells… leading to age-related gradual failure of the hematopoietic system. The loss of self-renewal of hematopoietic stem cells not only leads to anaemia and immunosenscence but also leads to the emergence of mutated clones, a process known as clonal haematopoiesis, which increases cardiovascular risk. (19).

Likewise, the exhaustion of neural and mesenchymal stem cells has repercussions that go beyond local tissues. This decline is driven by chronic, low-grade inflammation, which disrupts quiescence and exhausts progenitors. According to Frontiers in Immunology, IL-6 and TNF∝ are inflammatory cytokines that drive myeloid skewing and impair self-renewal, producing long-term defects in regeneration. Muscle cells of elderly people show denervation and differentiation changes due to Notch and Wnt signalling changes, as per (20).

A gradual loss of muscle mass and strength results in sarcopenia and frailty.
With time, the aggregate failure of stem cells gives rise to an age-associated universal phenotype not restricted to any tissue,e but affects immunity, metabolism, cognition, and musculoskeletal health. As the function of stem cells deteriorates and their niches become deregulated, organ systems become less resilient to disease. The exhaustion of stem cells connects seemingly unrelated diseases commonly associated with ageing. It alters local cellular senescence into a whole-system decay hallmark of ageing itself.

IV. CONCLUSION AND PROSPECTS

Stem cell exhaustion is a problem that connects many diseases that happen when we get older. These diseases do not seem to be related, but stem cell exhaustion is a common link between them. When the cells in our body get old and tired, it affects the body, and we start to feel the effects of ageing. Stem cell exhaustion is both a result of ageing and a cause of it. As we get older, the cells that help our body repair itself start to run out. The places where these cells live become inflamed and scarred. This means our body has a time fixing itself and staying healthy. Stem cell exhaustion is a part of why our body starts to decline as we get older. This problem is clear when

we look at things like sarcopenia, osteoarthritis and neurodegeneration. We also see it when older people get cancer because their cells are more likely to have mistakes in them. At first, the cells in our body have a time staying healthy. Over time, this can lead to many parts of our body not working properly.

However, some new discoveries suggest that this decline is not inevitable. Some experiments have tried to stop inflammationine the environment around stem cells, or change the way cells work a bit. These experiments have shown that it is possible to make old tissues work better again. The idea is to help the body repair itself as it used to when we were younger. This is what happens when we try to restore the ability of tissues to regenerate, like sarcopenia, osteoarthritis and neurodegeneration. These advances suggest that stem cell exhaustion may not be an irreversible hallmark, but a modifiable one.

In conclusion, understanding stem cell exhaustion provides a powerful framework for linking ageing with disease. It reframes ageing not as a passive wear, but as an active, cellularly governed process, one that could, in theory, be delayed or even partially reversed. The future of regenerative medicine may well depend on our ability to restore what ageing has taken away: the lifelong capacity to repair and renew.

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